

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

To:
J. PETER FASSE
FISH & RICHARSON
225 FRANKLIN STREET
BOSTON, MA 02110-2804

RECEIVED

JUL 08 2002

**FISH & RICHARDSON, PC.
BOSTON OFFICE**

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 01886-071WO1	Date of Mailing (day/month/year) <div style="text-align: center;">28 JUN 2002</div>
International application No. PCT/US02/05379	International filing date (day/month/year) 20 February 2002 (20.02.2002)
Applicant VYSIS, INC.	FOR FURTHER ACTION See paragraphs 1 and 4 below

Received by: *[Signature]*
 Date: *8/28/02*
 Initials: *SPM*
 Foreign Art: *9/12/02*

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Commissioner for Patents
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
[Signature]
Sally Sakelaris

Telephone No. 703-308-0196

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
J. PETER FASSE
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BOSTON, MA 02110-2804

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

28 JUN 2002

Applicant's or agent's file reference
01886-071WO1

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US02/05379

International filing date
(day/month/year)

20 February 2002 (20.02.2002)

Applicant
VYSIS, INC.

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Authorized officer
Sally Sakelaris

Telephone No. 703-308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 01886-071WO1	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/05379	International filing date (<i>day/month/year</i>) 20 February 2002 (20.02.2002)	(Earliest) Priority Date (<i>day/month/year</i>) 20 February 2001 (20.02.2001)
Applicant VYSIS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (See Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5, and combination of two probes, 5p and 8q24 locus specific probe

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05379

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C12Q 1/68; C12P 19/34; C07H 21/04 US CL : 435/6, 91.2; 536/24.31, 24.33 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/6, 91.2; 536/24.31, 24.33 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST, STN		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,670,314 A (CHRISTMAN et al.) 23 September 1997 (23.09.1997), column 10, table 1, column 9, lines 44-48, column 10, lines 5-8	1-5
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"I"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 07 June 2002 (07.06.2002)		Date of mailing of the international search report 28 JUN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Sally Sakararis Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05379

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1-16, Claims 1-5, drawn to a combination of two probes as set forth in Claim 1, parts a) thru e). For example, if Applicant elects Group 1, then the probe set of a 5p chromosome arm probe and an 8q24 locus specific probe will be searched. Similarly, if Group 2 is elected then the probe set of a 5p chromosome arm and a 3q chromosome arm probe will be searched. In the same way, if Group 16 is elected a chromosome 6 enumeration probe and a chromosome 7 enumeration probe will be searched. Upon election, please specify the specific probe set to be searched.

Groups 17-25, Claim 6, drawn to a combination of three probes as set forth in parts a) thru e) of Claim 6. For example, if Applicant elects Group 17, then the combination of a 5p15 locus specific probe, a 8q24 locus specific probe, and a 9p21 locus specific probe will be searched.

Groups 26-36, Claim 7, drawn to a combination of four probes as set forth in parts a) thru k) of Claim 7. For example, if Applicant elects Group 26, then the combination of a 5p15 locus specific probe, a chromosome 6 enumeration probe, a 17p13 locus specific probe, and a chromosome 17 enumeration probe will be searched.

Groups 37-52, Claims 8-11, drawn to a method of screening for lung cancer in a subject using a combination of two probes. For example, if applicants elect Group 37, then methods of screening for lung cancer using a 5p chromosome arm probe and a 8q24 locus specific probe will be searched. In the same way, if Group 52 is elected a chromosome 6 enumeration probe and a chromosome 7 enumeration probe will be searched.

Groups 53-57, Claims 12-15, drawn to a method of screening for lung cancer in a subject comprising obtaining a chromosomal probe selected from 5p15, a chromosome enumeration probe, 7p12, 8q24 and a chromosome 9 enumeration probe respectively.

Groups 58-66, Claim 16, drawn to a method of screening for lung cancer in a subject using a combination of three probes. For example, if Applicant elects Group 58, then methods of screening for lung cancer using the combination of a 5p15 locus specific probe, a 8q24 locus specific probe, and a 9p21 locus specific probe will be searched.

Groups 67-77, Claims 17-19, drawn to a method of screening for lung cancer in a subject using a combination of four probes. For example, if Applicant elects Group 67, then the methods of screening for lung cancer using the combination of a 5p15 locus specific probe, a chromosome 6 enumeration probe, a 17p13 locus specific probe, and a chromosome 17 enumeration probe will be searched.

Group 78, Claim 20, drawn to a method of selecting a combination of probes for the detection of cancer.

The inventions listed as Groups 1-78 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The composition of group 1 includes 2 probes comprising the sequences of the 5p chromosome arm and a 8q24 locus specific probe. Christman et al. teach "compositions and methods for detecting chromosome abnormalities correlated with lung cancer(US5670314, 9/1997)." The reference teaches a composition consisting of two probes comprising the sequences of the 5p chromosome arm and a 8q24 locus specific probe whose selective binding, and subsequent detection, to these target polynucleotide sequences is correlated with lung cancer. As the composition of claims 1-5 do not represent a contribution over the prior art, the

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05379

claims lack a special technical feature of the other claimed inventions. Thus, there is no special technical feature linking the recited compositions and methods of using said compositions, as would be necessary to fulfil the requirement for unity of invention.

Furthermore, it is also noted that each of the present claims has been presented in improper Markush format, as distinct products and distinct methods are improperly joined in the claims. Each composition of probes comprises 1,2,3, or 4 distinct probes. The probes each consist of a unique nucleotide sequence and differ in their structural and functional properties. Additionally, each combination of probes is distinct from the other in that each combination comprises probes of distinct structure and as a whole each combination is functionally distinct over each other. Each combination of probes has a different special technical feature. As the claimed compositions and methods using said compositions do not share a special technical feature, the distinct compositions and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the elected invention from the compositions of Groups 1-16, 17-25, and 26-36 which require different sets of chromosomal probes comprising combinations of 1,2,3, or 4 locus specific probes and are useful for detecting the hybridization pattern of the set of chromosomal probes to the biological sample to determine whether the subject has lung cancer. For example, Group 1 includes 2 probes comprising the sequences of the 5p chromosome arm and a 8q24 locus specific probe, whose specificity provides for the enhanced detection of lung cancer over conventional methods. the invention of the elected group.

Further, the claimed methods of groups 37-52, 53-57, 58-66, and 67-77, and 78 have different objectives, require different process steps and require the use of different reagents. The methods of Groups 37-52, 53-57, 58-66, and 67-77 require the steps of screening for lung cancer in a subject by obtaining a biological sample, obtaining one set of the aforementioned chromosomal probes, contacting the chromosomal probe to the biological sample and detecting the resulting hybridization to determine whether the subject has lung cancer. Each of the methods of groups 37-52, 53-57, 58-66 and 67-77 require the use of different reagents, i.e. a distinct combination of probes. The method of Group 78 requires the selection of chromosomal probe combinations by determining the ability of each of a first plurality of probes to distinguish cancer specimens from normal specimens yielding a second plurality of probes, wherein the second plurality of probes each identify the cancer specimens as compared to the normal specimens at a p value of less than 0.01 or a vector value of less than 0.500 and determining the ability of a combination of probes selected from the second plurality of probes to distinguish the cancer specimens from the normal specimens; and finally selecting a combination of probes that identifies the cancer specimen as compared to the normal specimen with a vector value of less than 0.400. In addition to differences in objectives, effects, and method steps, it is again noted that the claims of the present Groups are not directed to the detection or identification of molecules having the same or common special technical feature, for the reasons discussed above.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report, may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.